STUDIES TOWARDS THE DEVELOPMENT OF ASYMMETRIC ORGANOCATALYZED 1,4-CONJUGATE ADDITION REACTIONS IN AQUEOUS MEDIA

By

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August 2018

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SYNOPSIS

Broad Field of Research: "**Synthetic Organic Chemistry"**

Proposed Title: **"Studies towards the development of asymmetric organocatalyzed 1, 4-conjugate addition reactions in aqueous media"**

The development of enantioselective transformations has been the subject of numerous research effort in recent years (both economic and environmental point of concern), and in this context, a variety of efficient asymmetric catalysts for different organic reactions has been introduced.[1] With a few notable exceptions, however, the development of chiral ligands and catalysts for asymmetric synthesis has been carried out almost exclusively in organic media under absolute anhydrous conditions.[1] But, Last 5-10 years, water has found its way as a potential alternative solvent for stereoselective organic transformations.[2] As far as the environmental pollution is concerned, there could never be a better option than water as solvent, since a large volume of flammables and carcinogenic organic solvents, major contributors to the environmental pollution, are being used in pharmaceuticals and other industries. Moreover, cost and safety are the other advantageous factors in favour of water. Indeed, water is a safe, harmless, and environmentally benign solvent. In addition, from practical and synthetic standpoints, a benefit of using water is immediately evident as it is not necessary to dry solvents and substrates for the reactions in aqueous media, and aqueous solutions of substrates or hydrated substrates can be directly used without further drying. Moreover, water has unique physical and chemical properties, such as high dielectric constant and high cohesive energy density relative to most organic solvents. By utilizing these properties, highly efficient and selective enzymatic reactions are conducted in living systems under mild conditions. Notably, the medium of enzymatic reactions is water, which plays major roles in the reactions. If the unique nature of water could be utilized *in vitro* as it is *in vivo*, it would be possible to develop interesting reactions with unique reactivity and selectivity that cannot be attained in organic solvents. At the outset, aqueous organic reactions have broad applications such as synthesis of biological compounds from carbohydrates and chemical modification of biomolecules. Therefore, it has become an unavoidable necessary to develop more and more methodologies for asymmetric organic

transformations in water. In this perspective, in certain instances, however, some water-stable chiral catalysts have been developed, still preparation and applications of highly efficient, robust and water-stable chiral catalysts for several asymmetric transformations, is a challenging area of study.

Asymmetric organocatalysis, a metal free catalysis is currently a widely used environmentally benign catalytic methodology in asymmetric organic synthesis.[3] Last two decades have witnessed an explosive growth in the field of asymmetric organocatalysis where water has been used as a solvent or co-solvent.[4] The pioneering observation reported by Breslow et al. and Grieco et al. on Diels–Alder reaction in early 1980s revealed the new concept regarding the better effect of water on reaction rates and regioselectivities than organic solvents.[5] Apart from safety, cost and environmental issue, water can significantly influence the course of a chiral organocatalyzed reaction *via* increased hydrophobic-hydrophobic interaction and hydrogen bond formation between the reactants and water molecules resulting high reactivity and stereoselectivity.[6] Since the Breslow's observation, existence of such interactions and their effects are now a well documented fact in aqueous phase reactions irrespective of "in water" or "on water" concept in back ground.[7] In the past few years a great deal of attention devoted to the naturally occurring amino acids due to both of its low cost and high enantiopure availability and in particular, massive efforts have been concentrated on the development of L-proline and 4-hydroxy-L-proline based organocatalysts, primarily modifying their basic skeleton in three ways.[8] One modification was aimed at the carboxylic acid functionality[9], one was performed on hydroxyl group of 4-hydroxy-L-proline[10] and while the third one was on both groups simultaneously[11]. In addition to the oragnocatalysts derived from L-proline and 4-hydroxy-L-proline, a broad variety of chiral organocatalysts too can be developed from many other natural molecules like (+)-Tartaric acid, (-)-Ephedrine etc. It is being recognized that a combination of chiral organic molecules as catalysts and water as a medium can promote various asymmetric C-C bond forming reactions e.g. aldol reaction, 1, 4-conjugate addition, allylation to carbonyl compounds, Mannich reaction, Diels-Alder reaction etc. But more than 80% of total reports on asymmetric organocatalyzed carbon-carbon bond-forming reactions in aqueous media have been on aldol reactions.[12]

In the present context, our prime focus would be to develop new optically pure organic molecules which can be applied as organocatalysts in 1, 4-conjugate addition reactions in aqueous media. Since these reactions are in a preliminary stage of development in aqueous media, an immediate research is thus very much necessary.

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